Assessing Cancer Risk & Assuring Safe Use of Topical Immunosuppressants: Recent History

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Today's Talk—the Chronology

- Describe the context leading to the October, 2003 Meeting
- Summarize from that Meeting:
  - The Epidemiologic Design Issues and Constraints
  - The Key Points from the Committee Discussion
- Describe the Current Landscape

Before October 2003

Prograf ® (tacrolimus)
Oral & Intravenous Formulation

- Approved April 1994
- Indication:

  "prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplants."

- Boxed warning about susceptibility to infection and possible development of lymphoma:

WARNING

Increased susceptibility to infection and **the possible development of lymphoma may result from immunosuppression**. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf ®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Topical Immunosuppressant Calcineurin Inhibitor Class

- Two products
  - Protopic® (tacrolimus) Ointment 0.03% & 0.1%
    Approved December 2000
  - Elidel® (pimecrolimus) Cream 1%
    Approved December 2001
- Approved for atopic dermatitis in children 2 years & older
  - Tacrolimus Ointment— *moderate to severe* AD
  - Pimecrolimus Cream---*mild to moderate* AD
- Mechanism of action in atopic dermatitis unknown
- *"Classical Immunosuppressant"*

Positive Animal Carcinogenicity Studies Before October 2003

- Tacrolimus Ointment
  - Lymphoma signal in dermal mouse carcinogenicity study
- Pimecrolimus Cream
  - Lymphoma signal in oral mouse carcinogenicity study
  - Lymphoma signal in 13 week dermal mouse study (pimecrolimus dissolved in ethanol)
- Pimecrolimus Cream—other tumor signals:
  - Benign thymoma in oral rat carcinogenicity study
  - Follicular cell adenoma of the thyroid in dermal rat carcinogenicity study

Post Marketing Commitments for Registry Studies to Assess Cancer Risk in Pediatric Patients in Approval Letters

- Tacrolimus Ointment

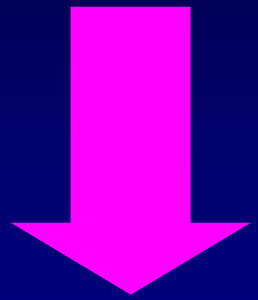
> "A commitment to conduct a registry study of pediatric patients with atopic dermatitis to address the risk of developing cutaneous or systemic malignancies in patients who have long term intermittent treatment with Protopic Ointment 0.03% or 0.1%."

- Pimecrolimus Cream

> "We agree to conduct a registry study of pediatric patients (aged 2-17, with emphasis on the younger ages) with atopic dermatitis followed through adulthood for those who have long-term intermittent treatment with Elidel (pimecrolimus) 1% Cream to assess the risk of developing systemic malignancies."

Complexities of Post Marketing Studies Recognized

Solution



Consult the Advisory Committee

October 30, 2003

The October 2003 Meeting

Topics Discussed—October 2003

- Product Review
- Animal Toxicity
- Post Marketing Adverse Event Reports
- Registry Design Presentations
  - Study Designs for the Phase 4 Studies
  - Practical and Methodological Issues
  - Role of Cancer Registries
- Discussion of Questions by Committee

Complexities & Uncertainties about Registry Studies Unresolved

- Difficulty with measuring & quantifying:
  - Exposure to topical drug product
  - Confounding variables
  - Cancer outcomes
- Lack of skin cancer ascertainment in population registries
- Long latency between exposure & cancer requires studies of at least 10 to 15 years
- Substantial cost to track and assure high retention rates
- Rarity of cancer in children & youth requiring very large cohort
- Need to maximize retention for valid results

Oct 2003 Committee Discussion of Risk Management

- Concern that prescribers & public lack awareness of potential risk
  - "*We need to better inform patients and physicians about all of these issues related to these drugs… this information needs to be made more public than it has been.*"
- Need to better assure use as labeled
  - "*as second-line drug when really needed, not rely on it chronically*"
- Discussion about strengthening warnings (including box) & applying other risk communication tools-- though no vote.

From October 2003 to Now (with proposals for the future)

Animal Carcinogenicity, Human Cancer Cases, Increasing Use

- Oral Primate Carcinogenicity Study
  - Strongly positive for lymphoma
  - Dose-response effect
- Additional reports of cancer and other serious adverse events in children & adults
- Increasing use of pimecrolimus cream & tacrolimus ointment, including in children younger than 2 years
- Limited progress in establishment of registries

Recent Themes in the Dermatology, Pediatrics & Allergy Literature

- Use Tacrolimus & Pimecrolimus for first-line therapy
- Use Tacrolimus & Pimecrolimus continuously to prevent flares
- Use in children younger than 2 years is safe

Literature Examples

- *Patel RR, et. al. The safety and efficacy of tacrolimus therapy in patients younger than 2 years with atopic dermatitis. Arch Dermatol, 2003;139:1184-86.*
- *Ho VC et al. Safety & efficacy of non-steroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. J Pediatr 2003;142:155-62*
- *Boguniewicz M, Eichenfield LF, et al. Current management of atopic dermatitis and interruption of the atopic march. J Allergy Clin Immunol 2003 112: S140-50.*

The Current Landscape

- Unknown certainty about serious cancer risk
- May never be able to accurately quantify
- Additional animal carcinogenicity signals
- Additional human reports
- Medical literature about expanded use for off-label indications
- Increasing use